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09/627,383	07/28/2000	Paul T. Matsudaira	0399.1211-001	3215

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EXAMINER
COOK, LISA V

ART UNIT	PAPER NUMBER
1641	12

DATE MAILED: 07/30/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/627,383	MATSUDAIRA ET AL.	
	Examiner	Art Unit	
	Lisa V. Cook	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *1-10 and 16-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-15 and 27-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Amendment Entry

1. Applicants' response to the Office Action mailed 6 November 2001 in Paper #11, filed 5/21/02 is acknowledged. In amendment-A filed therein the specification along with claims 11-15 were amended. While new claims 27-29 were added. Claims 11-15 and 27-29 are under consideration.

Request for Corrected Filing Receipt

2. Applicants request to correct an error/inconsistency in priority data regarding provisional application no. 60/061,801 filed 10/14/97 is noted. Application number 60/061,801 filed 10/14/97 has been deleted in the continuing data as claimed by applicant.

OBJECTIONS WITHDRAWN

Priority

3. Provisional application no. 60/061,801 was filed more than one year to the filing of the instant application. (10/14/97). Benefit to this application is not granted. See MPEP 35 USC 119- 3 (e)(1). [as though filed on the date of the provisional application filed under section 111(b) of this title, if the application for patent filed under section 111(a) or section 363 of this title is filed not later than 12 months after the date on which the provisional application was filed and if it contains or is amended to contain a specific reference to the provisional application. No application shall be entitled to the benefit of an earlier filed provisional application under this subsection unless an amendment containing the specific reference to the earlier filed provisional application is submitted at such time during the pendency of the application as required by the Director.]

Benefit to provisional application no. 60/061,801 filed 10/14/97 has been vacated, therein the objection is withdrawn.

Oath/Declaration

4. A new oath or declaration is required because provisional application number 60/061,801, filed 10/14/1997 is not listed under 35 USC 119(e). The wording of an oath or declaration cannot be amended. If the wording is not correct or if all of the required affirmations have not been made or if it has not been properly subscribed to, a new oath or declaration is required. The new oath or declaration must properly identify the application of which it is to form a part, preferably by application number and filing date in the body of the oath or declaration. See MPEP §§ 602.01 and 602.02. *Priority is no longer claimed to application number 60/061,801 filed 10/14/97. Therefore the objection is withdrawn.*

Specification

5. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

I. The use of the trademarks has been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

Applicant has amended the specification to capitalize trademarks. The objection is withdrawn. Correction LVC 1/16/03
^ *maintained.*

Claim Objections

6. Claims 11-15 are objected to under 37CFR 1. 821(d) for failing to recite the SEQ ID NOS in the claims. Therein the actual compositions are not properly recited. Appropriate correction is required.

Applicants have amended the claims to recite SEQ ID NO:1, therein obviating the objection.

OBJECTIONS MAINTAINED

Drawings

7. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

Information Disclosure Statement

8. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the examiner on form PTO-892 or applicant on PTO-1449 has cited the references they have not been considered.

9. The information disclosure statement filed 3/22/01-Paper #6, has been considered as to the merits prior to first action. Further application number 60/061,801 filed 10/14/97 has been considered and indicated on page 2 of paper #6 filed 3/22/01..

REJECTIONS WITHDRAWN

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

10. Claims 11-15 are directed to non-statutory subject matter. The invention as claimed reads on an affinity fluorescent expression cassette/vector/molecule, which includes naturally occurring as well as synthetic compositions. Nonnaturally occurring compositions are considered to be patentable subject matter with in the scope of 35 U.S.C. 101, but products occurring in nature are considered non-statutory and non-patentable. See Official Gazette, 1077 O.G. 24, April 21, 1987. It is recommended that the claims incorporate the claim language, "isolated" or "purified" to overcome this rejection.

Applicants have amended the claims to recite "isolated". The rejections is withdrawn.

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

11. Claims 11and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 11 and 14 are not clear as to what end of the nucleic acid is the reference point from which to start counting from to determine the position of where to introduce the restriction nuclease sites. It is suggested that the actual sequence be recited in the claims for clarifying the instantly claimed structure.

B. Claim 11 is also confusing with respect to the phrase "restriction endonuclease sites introduced". Restriction endonucleases recognize specific sequences of nucleic acids to determine where they act on and cleave the nucleic acid. The phrase in question suggest insertion of the nucleic acid sequences recognized by restriction enzymes. If so it is not clear what nucleic acid sequences are being inserted. It is suggested that the actual sequence including the cleaved sites be recited in the claims for clarifying the instantly claimed structure and obviate this rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 11, 14, 27 and 29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case does not set forth any all possible mutations (detections and/or substitutions) to the GFP nucleic acid of the instsn claims therefore the written description is not commensurate in scope with the claims.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116). Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

The skilled artisan cannot envision the detailed structure of the encompassed all possible GFP nucleic acid mutations and the unlimited number of sequence configurations encompassed by the claims and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. (Please see instant disclosure page 13-15). The sequence of the structure itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016. Furthermore, In *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of a compound/seq.id/etc. by only their functional activity does not provide an adequate written description of the genus.

The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of molecules, usually defined by a sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description ...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". The disclosure provides insufficient support to the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

13. Claims 11, 14, 27 and 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide description of or enablement for any and every modified GFP nucleic acid sequence which is mutated.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Applicant provides guidance for specific embodiments covered by the seq id nos identified in the disclosure however the disclosure does not provides guidance as to all modifications or structures encompassed by the broad claims. The predictable structure ad function of the unlimited possible modifications to a GFP nucleic acid may exhibit very different structures not necessarily having with the same specificity. For example, very different V_H chains can combine with the same V_L chain to produce binding sites with nearly the same size, shape, antigen specificity, and affinity.

A similar phenomenon can also occur when different V_H sequences combine with different V_L sequences to produce with very similar properties. These observations indicate that divergent variable region sequences, both in and out of complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. Conversely, similar structure may be found to have different specificities.

In the absence of any guidance other than to the use of the sequences taught in the instant specification, one would not know or be able to predict any and all possible structures or modifications were important/read on the instant claims and the amount of experimentation required to determine the same combination of the structures would be undue. Note that an enabling disclosure for the preparation and use of only a few analogs of a product does not enable all possible analogs where the characteristics of the analogs are unpredictable.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

I. Claims 11, 13, 14, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsien et al. (WO 97/28261) in view of Tsien et al. (USC Patent #6,066,476) and further in view of Miesenbock et al. (WO 98/36081).

Tsien et al.(WO 97/28261) teach tandem fluorescent protein constructs including GFPs. (affinity fluorescent protein molecules) See abstract and page 14. A first polypeptide binding domain-donor fluorescent protein construct, an acceptor fluorescent protein moiety, and a second polypeptide binding domain-a linker moiety coupling the donor and acceptor (tandem fluorescent protein constructs) are employed to measure enzymatic activity. One of the components of this tandem fluorescent protein construct comprises a cleavage recognition site for an enzyme. (Page 2, lines 25-28). Fluorescence resonance energy transfer measurements can be determined when the donor moiety is excited. (Page 2, lines 16-30). Enzymatic activity assays are utilized to detect both *in vitro* and *in vivo* evaluations. See page 2, lines 16-18.

Tsien et al.(6,066,476) further disclosed that modification in the sequence of Aequorea wild-type GFP could provide products with different excitation and emission spectra's. Several different restriction endonuclease sites are discussed in the patent. See columns 4-6.

Tsien et al.(WO 97/28261) and Tsien et al.(6,066,476) differ from the instant invention in not specifically teaching the reaction sites recited in the claims (i.e. Gln157 and Lys158, etc).

However, Miesenbock et al. disclosed affinity fluorescent protein expression molecules comprising modified GFP (see figure 5 and page 25) Examples of amino acid substitutions are seen in table 2.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize various modified GFP sequences as taught by Miesenbock et al. in the GFP tandem constructs of Tsien et al. (WO 97/28261) in view of the modified GFPs of Tsien et al. to produce affinity fluorescent protein molecules because such restriction site modification procedures as taught by Miesenbock et al. are well known in the art. A person of ordinary skill in the art would have had a reasonable expectation of success utilizing endonuclease restriction in GFP sequence production as taught by Miesenbock et al. because fluorescent molecules were taught to be attractive as receptor molecules in many assay systems because of their high sensitivity and ease of quantification. See abstract.

A person of ordinary skill in the art would have been motivated to employ modified GFPs because Miesenbock et al. taught that such restriction modifications would further enhance the ability of the molecules to detect changes in the microenvironment. See page 4, line 35 to page 5, line 1. With respect to the particular restrict site, unless the result obtained in the instant application is a significant and unexpected difference over the prior art, it would have been prima facie obvious for one of ordinary skill in the art to modify GFP at known restriction sites in order to produce the most optimal configuration useful in the given parameters.

II. Claims 12 and 27-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsien et al. (WO 97/28261) and Tsien et al. (USC Patent #6,066,476) in view of Miesenbock et al. (WO 98/36081) and in further view of Gorman et al. (WO 99/19489).

Please see Tsien et al.(WO 97/28261) and Tsien et al.(6,066,476) in view of Miesenbock et al. (WO 98/36081) as set forth above.

Please see Tsien et al.(WO 97/28261) and Tsien et al.(6,066,476) in view of Miesenbock et al. (WO 98/36081) differ from the instant invention in not specifically disclosing sequence identification number 1.

However, Gorman et al. (WO 99/19489) disclose a composition comprising the specific sequence identification number 1 as Myosin IXa polypeptide sequence identification number 1. See abstract and pages 4-5.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize various modified GFP sequences as taught by Miesenbock et al. comprising seq id no 1 as taught by Gorman et al. in the GFP tandem constructs of Tsien et al. (WO 97/28261) in view of the modified GFPs of Tsien et al. (6,066,476) to produce affinity fluorescent protein molecules because such restriction site modification procedures as taught by Miesenbock et al. comprising seq id no 1 as taught by Gorman et al. because Miesenbock et al. taught that fluorescent molecules attractive as receptor molecules in many assay systems because of their high sensitivity and ease of quantification. See abstract.

While, Gorman et al. taught that sequence identification number 1 (Myosin IXa activity) is involved in several immunological events (ATP binding, ATPase, zinc binding, calmodulin/EF binding, G-coupled receptors, membrane binding, modulation of cell interacts, calcium release, cytoskeletal rearrangements, etc.-see page 10-11).

A person of ordinary skill in the art would have been motivated to employ modified GFPs because Miesenbock et al. taught that such restriction modifications would further enhance the ability of the molecules to detect changes in the microenvironment. See page 4, line 35 to page 5, line 1. Gorman et al. disclose expression vectors wherein Myosin IXa (seq id no 1) is linked to a signal sequence for selected markers are convenient. See page 18-22, esp page 21 line 20-28. With respect to the particular restrict site, unless the result obtained in the instant application is a significant and unexpected difference over the prior art, it would have been prima facie obvious for one of ordinary skill in the art to modify GFP at known restriction sites in order to produce the most optimal configuration useful in the given parameters.

Response to Argument

Applicant contends that the cited references did not in clued modified GFP sequences comprising a recombinant peptide which comprises restriction endonuclease sites introduced at a location of the GFP molecule (seq id no 1). This argument was carefully considered and found persuasive. The reference to Gorman et al. was cited because it disclosed seq id no 1. Therein meeting the recombinant peptide compositions claimed.

15. For reasons aforementioned, no claims are allowed.

Remarks

16. Prior art made of record and not relied upon is considered pertinent to the applicant's disclosure:

Tsien et al. (WO 92/00388) teach long wavelength engineered fluorescent proteins and their methods of use. Fluorescent molecules are attractive as reporter molecules in many assay systems because of their high sensitivity and ease of quantification (page 1, lines 15-16).

Thastrup et al.(US patent 5,958,713) disclose modified GFP proteins to detect biological activity.

17. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 Fax number is (703) 308-4242, which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (703) 305-0808. The examiner can normally be reached on Monday-Friday from 8:00 AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (703) 305-3399.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Lisa V. Cook
CM1-7B17
(703) 305-0808
7/22/02

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP ~~1800~~ 1641

Statement Under 37 CFR 1.97(e)

[ ] Each item of information contained in this Information Disclosure Statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Information Disclosure Statement; or

[ ] No item of information contained in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the undersigned, after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of this Information Disclosure Statement.

Statement Under 37 CFR 1.704(d) (Patent Term Adjustment)

[ ] Each item of information contained in the Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart application and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the Information Disclosure Statement.

[X] Enclosed herewith is form PTO-1449:

[X] Copies of the cited references are enclosed (AA-AH, AL-AO and AR-AZ; AR2).

[ ] Copies of cited references are enclosed except those entered in prior application, U.S. Application No. [ ], to which priority under 35 U.S.C. 120 is claimed. [The earlier application contains copies of the cited references.]

[X] The listed references (AA-AB, AL-AO and AR2) were cited in the enclosed International Search Report in a counterpart foreign application.

Concise Explanation Requirement (non-English references):

[ ] The "concise explanation" requirement for reference(s) [ ] under 37 CFR 1.98(a)(3) is satisfied by:

[ ] the explanation provided on the attached sheet.

[ ] the explanation provided in the Specification.

[ ] submission of the enclosed International Search Report.

[ ] the enclosed English language abstract.

[X] Applicant requests that the following pending applications be considered:

Examiner's Initials

LVC

U.S. Patent Application No. 60/061,801, by Paul T. Matsudaira, *et al.*, filed October 14, 1997, Docket No.: 0039.1172-000

Lisa A. Cook
Examiner

7/22/02
Date

[X] A copy of each above-cited application is enclosed.

The Examiner is requested to return a copy of the above list of pending applications indicating which references were considered with the next office communication.

It is requested that the information disclosed herein be made of record in this application.